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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Don D. Cha
547 Buena Vista Road
Golden, CO 80401

EXAMINER	
MOORE, WILLIAM W	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/518,081	SHAPIRO, LELAND	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40 and 43* is/are rejected.

7)☒ Claim(s) *41 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20010504*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's Response filed 22 January 2008 has been entered, amending claims 33 and 43. A supplemental Amendment filed 21 April 2009 has not been entered. The amendments of claims 33 and 34 clarify the intended subject matters and overcome the objection of record of both claims stated in the communication mailed 4 September 2008. Together with Applicant's arguments, the claim amendments and the publications submitted as Exhibits A through E on 22 January 2009, overcome the rejections of record of claims herein under 35 USC § 112, first paragraph, for lack of adequate written description and for lack of enablement for the reasons discussed below. Application No. 10/427,929 is neither pending nor issued as a patent, thus the provisional rejection of record of claims herein for nonstatutory double patenting rejection over the claims of that application is WITHDRAWN. In view of the singular difference between the recitations of the amended claims 33 and 43 – where both are drawn to methods of treatment comprising administration of α_1-antitrypsin [AAT] but claim 33 requires inhibition of apoptosis while claim 43 does not – this application's prosecution history is reviewed with regard to issues of written description, enablement, and the prior art previously applied in rejections now withdrawn. This communication is not made final because new grounds of rejection are stated hereinbelow.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed 4 May 2001 has been considered in the preparation of this communication to the extent indicated in the executed copies of its twelve pages of Forms PTO-1449 that accompany this communication. Some cited journal articles were not supplied with the IDS - Cox et al. 1991, Di Ianni et al. 1994, Popko et al. 1999, and Szegy et al. 1968 - but each was found in the file of a related application and considered.

35 USC § 112, first paragraph, Rejections Withdrawn

Written Description and Enablement: Applicant does not separately address the different rejections of claims herein for lack of an adequate written description and for lack or enablement at pages 4-6 of the Response filed 22 January 2009. Both issues are taken together herein. It is clear that the specification identifies (i) the several diseases and medical conditions recited in claims 33, 42, and 43 at, e.g., lines 5-10 of page 14, (ii) the several variants of AAT indicated in claims 33 and 43 in the paragraph spanning pages 5 and 6, (iii) the ranges and frequencies of dosage of claims 36-39 and 41, and modes of administration of AAT recited in claim 40, at lines

11-31 of page 7, lines 1-10 of page 8, lines 14-18 of page 14, lines 6-22 of page 15, and lines 5-16 of page 16, and (iv) the co-administration of functionally-defined components of claim 35 at lines 24 and 25 of page 8 and at lines 2-6 of page 17.

Inhibition had been narrowly construed in the prosecution of this application, e.g., as distinct from reduction.[1] Inhibition is now construed more broadly herein to restrain,[2] to restrict,[3] or to interfere[4] with apoptosis. The written description rejection of record and the enablement rejection of record were stated because the specification did not show that AAT could contact, thus potentially inhibit, the intracellular proteases that the specification discloses, at page 2, to be involved in apoptosis.[5] Neither of these rejections of record can be maintained in view of the publications of Petrache et al. October 2006 and Petrache et al. March 2006, made of record with the communication mailed 1 April 2008, and of Tuder et al., Daemen et al., Beard et al., and Taraseviciene-Stewart et al., each made of record herewith, as well as van Molle et al., made of record with the IDS filed 4 May 2001 and applied as prior art in the communication mailed 14 January 2002.

Petrache et al. October 2006 show that AAT can inhibiting the proteolytic activity of at least one intracellular component of the apoptosis process, the cysteine protease caspase-3, in a cell-free system and Petrache et al. March 2006 show that introducing AAT within cells - using an adenonviral vector expressing AAT in alveolar cells - inhibits apoptosis caused by blocking the cell-surface vascular endothelial cell growth receptor. While Daemen et al. do not exclude an "interact[ion by AAT] with the proteolytic cascade of enzymes involved in apoptosis" in their discussion in the right column of page 1423, neither do they indicate that AAT is internalized in kidney cells in inhibiting apoptosis in mouse kidneys in response to ischemia/reperfusion injury where AAT is administered intraperitoneally concomitant with reperfusion, and further suggest that, while intraperitoneal administration two hours after reperfusion does not prevent primary apoptosis, secondary apoptosis is reduced due to possible involvement of "an anti-inflammatory effect" in the paragraph spanning pages 1421-1422. Van Molle et al. show that intraperitoneal injection of AAT was adequate to inhibit apoptosis *in vivo* in mouse hepatocytes, but not all liver cells, mediated by joint exposure to tumor necrosis factor-α [TNFα] and galactosamine, but not

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[1] Communication of 14 January 2002, first sentence of paragraph of item 18 at page 10.

[2] "inhibit" definition 2a: "to hold in check; RESTRAIN", Webster's Ninth New Collegiate Dictionary, 1990.

[3] "inhibition" definition 1b: "something that . . . restricts, Webster's Ninth New Collegiate Dictionary, 1990.

[4] "inhibitor" definition: "that slows or interferes with a chemical reaction", Webster's Ninth New Collegiate Dictionary, 1990.

[5] Communication of 9 January 2007, pages 4 and 5.

apoptosis mediated by joint exposure to TNFα and actinomycin D, teaching that negative results in an *in vitro* control conducted with an hepatoma cell line "suggests that [AAT] confer[s] *in vivo* protection by an indirect mechanism."

Two of the publications that Applicant submitted with the Response filed 29 January 2003, and made of record with this communication, indicate that modifying signals that commence at the cell surface can induce apoptosis, suggesting that interfering with adverse signals at the cell surface, or extracellularly, may restrict apoptosis. Bogden et al. show that an intracisternal administration of a TNFα-specific monoclonal antibody [mAb], blocking TNFα's interaction with cells *in vivo* in the rat central nervous system exposed to meningitis-inducing streptococci, protected neurons in a region of the hippocampus, but not in the cortex, of the rat brain and that even intraperitoneal, i.e., systemic, administration of the TNFα-specific mAb offered some protection for hippocampal neurons. See Figures 1-3 and their captions. In sections captioned "Extracellular Death Ligands and Receptors" and "Death by Neglect", Hetts generally discusses extracellular mechanisms influencing apoptosis at pages 301 and 302. The record shows that at the time the invention was made artisans recognized that a pharmaceutical polypeptide, such as AAT, need not necessarily inhibit apoptosis by inhibiting intracellular proteases involved in apoptosis, such as caspase 3, thus the specification need not describe or teach delivery of AAT to an intracellular compartment of cells in a tissue affected by a disease or medical condition of 33 and 43 to adequately describe or enable a claimed invention. Consequently, claim 33's additional limitation, "inhibits apoptosis", is not considered to distinguish its subject matter from that of claim 34 where administering AAT may affect a physiological process associated with apoptosis and inhibit it by an indirect mechanism, such as reducing inflammation.[6] The rejections of record are therefore WITHDRAWN.

Objection: Drawing Figure/Specification

While the Formal Drawings filed 23 January 2004 were accepted in the communication mailed 29 June 2005, and the specification states a description of Figure 1 at page 6, the terms of the conditions stated in Figure 1 are not reflected in any discussion at pages 17-19 of the specification of apoptosis and rat cerebral granule cells, the best basis in the specification for the acronym "RCGC" in the Drawing Figure 1. Specifically the time interval stated in Figure 1 is not stated in the specification. Thus the Drawing Figure 1 is objected to. This objection may be

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[6] See Déry et al. 1999, made of record with Applicant's IDS filed 4 May 2001, particularly page 249's discussion of activation of the cell surface PAR-2 receptor by trypsin cleavage when the protease is expressed by endothelial cells, as well as by pancreatic cells, in inflammation.

overcome either by demonstrating inherent support in the specification for the terms used in the Drawing Figure, amending the Drawing Figure to state terms actually disclosed in the specification, or cancelling the Drawing Figure 1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33-41 and 43 remain provisionally rejected for reasons of record on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-46 of copending Application No. 12/051,373. Although the conflicting claims are not identical, they are not patentably distinct from each other because, whether apoptosis is inhibited according to claims 33-41 herein or such inhibition is not particularly required according to claim 43 herein, a method for treating an autoimmune disease of claims 31-41 and 43 herein is also a method of the copending claims of treating diabetes, where Type 1 diabetes is an autoimmune disease, by administering "α_1-antitrypsin or derivative thereof". While Applicant requests at page 4 of the Response that the issue of nonstatutory obviousness-type double patenting be deferred until an indication of allowable subject matter occurs, this rejection of record is maintained until and unless a Terminal Disclaimer is filed. This rejection may be withdrawn should this application issue as a patent before the copending application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 36, 40, and 43 are rejected under 35 USC § 102(b) as being anticipated by Lezdey et al., US 5,346,886.

Lezdey et al. disclose a transdermal application of AAT to subjects - persons - in treating "inflammatory skin conditions including those which are induced by autoimmune disease", where transdermal transfer of AAT is facilitated by incorporation of either or both of ethoxylated nonylphenol and benzalkonium chloride in a pharmaceutical composition, meeting limitations of claims 33, 36, 40, and 43. See col. 3, lines 15-32, col. 4, lines 34-36 and 44-48, col. 5. lines 7-9, the first line of each formula in cols. 5-10, and col. 10, lines 30-42.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 USC § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-40 and 43 are rejected under 35 USC § 103(a) as being unpatentable over Lezdey et al., US 6,124,257, of record, and Lezdey et al. US 5,780,440, in view of Scott et al. US 5,187,089, and Barker et al., 1997, all made of record herewith.

Lezdey et al. '257 teach that "[d]uring surgery such as heart surgery there is reperfusion or perfusion injury [and s]ince mast cells are present in and around the heart tissues and there is an inflammatory response, elastase is released", and further teach that AAT binds and inhibits neutrophil elastase and "is known to inhibit the degranulation of [ ] mast cells", reducing the inflammatory response. See col. 1 at lines 63-66 and col. 3 at lines 19-26. Lezdey et al. '440 teach the therapeutic co-administration of an elastase inhibitor, including AAT, together with glutathione as an "oxygen metabolite", i.e., a free radical, "scavenger". See claims 1-3, particularly claim 2. While Lezdey et al. '257 teach a protective role of AAT in reperfusion injury, neither of Lezdey et al. '257 nor Lezdey et al. '440 teach the intramuscular or intravenous administration of AAT together with glutathione in a method of treating a medical condition, nor an appropriate dosage of AAT and administration frequency, thus Scott et al. '089 are now cited for teaching the intravenous and intramuscular administration of a polypeptide elastase inhibitor for the treatment of arthritis and other elastase-related diseases. See col. 14, lines 28-33 and

lines 51-59. Barker et al. are now cited for teaching the biweekly intravenous administration of AAT at a dosage of 120 mg/kg to attain a desired serum concentration of 80mg/dL in order to treat a disease condition, and for teaching that a more frequent administration of AAT may be desirable. See abstract and the final paragraph of the right column at page 612.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to intravenously or intramuscularly administer AAT to a person to treat the medical conditions of arthritis and reperfusion injury according to claims 33, 36, 40, and 43 because it is a well-know inhibitor of the proteolytic activity of elastase, an activity which Lezdey et al. '257 teach contributes to reperfusion injury and that Scott et al. teach contributes to arthritis and obvious as well to administer AAT in amounts meeting the limitations of claim 34 to achieve concentrations meeting the concentrations in blood of claims 37-39 because Barker et al. teach intravenous administration of AAT in such amounts to achieve such concentrations in blood is worthwhile for treating a disease state mediated by the proteolytic activity of elastase. It would further have been obvious to such an artisan to administer AAT with the free radical scavenger glutathione because Lezdey et al. '440 teach that such co-administration is advantageous. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

Claims 41 and 42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art made of record herewith, Barker et al., cited above, and Smith et al., Casolaro et al., and Hubbard et al. made of record on the accompanying PTO-Form 892, uniformly teach intravenous administration schedules on the order of weeks, rather than days while the administration mode of Lezdey et al. '886 is continuous, thus more than once hourly. While there is no exemplification in the specification of treatment of the neurodegenerative diseases recited in claim 42, section 6.5 of the specification at pages 17 and 18 and Figure 2 indicate that the addition of AAT is protective *in vitro* against apoptosis of certain neuronal cells induced by serum depletion.

Lezdey et al., US 6,566,331, was made of record with the communication mailed 5 April 2006 and cited as prior art therein under 35 USC § 102(e). None of claims 33-43 as amended 22 January 2009 herein retain the amendment that Applicant had introduced 11 September 2006 to the original claim 1 requiring "monitoring a decrease in apoptosis" in order to avoid the

rejection of record over Lezdey et al. '331. The original claim 1 corresponds to claims 33 and 43 herein, yet the claims pending herein may not properly be rejected over the '331 patent because a review of the 1 February 1999-filed priority application of Lezdey et al., serial No. 09/241,754, found no basis therein for supporting the limitations of claims 1 and 7 of the '331 patent that together describe a "method of treating mammals suffering from collagen related disease selected from . . . **rheumatoid arthritis** which comprises administering a protease inhibitor . . . alpha 1-antitrypsin . . . in a suitable pharmaceutical carrier" (emphasis supplied). The '754 application has no discussion or mention of arthritis and the term "collagen related diseases" occurs but once in the '754 specification, at page 1, in referring to interstitial cystitis. By comparison, Applicant's 5 March 1999-filed provisional application 60/123,167 supports the terms recited in describing the methods of at least claims 33, 36, 38, 40, 41, and 43 herein at pages 19, 20, and 36-40. Thus Lezdey et al. '331 cannot be considered to be prior art to an invention claimed herein.

Daemen et al., US 6,924,267 is made of record herewith because, while it is not prior art to an invention claimed herein as it issued on an application filed 18 September 2001, it presents claims 1-8, 11, 12, and 17-23 to subject matter that corresponds substantially to the subject matter stated in claims 33, 34, 36-40, and 43 herein as amended 22 January 2009.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Andrew Wang, can be reached at 571.272.0811. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/William W. Moore/
Examiner, Art Unit 1656